REMARKS

I. Response to January 25, 2007, Office Action

Claims 59, 60, 65, 66, 69-74, 79, 125, 127-129, 133, 135-137, and 147-155 are pending in the application. No substantive claim amendments (a grammatical error was corrected in Claim 65, *See* corresponding claim amendment) and no new claims are being presented in response to the Office Action. The amendment to claim 65 presents no new matter.

Claims 59, 60, 65, 66, 69-74, 79, 125, 127-129, 133, 135-137, and 147-155 are currently rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Application Publication No. 20040136951 to Ni et al. (hereinafter referred to as "the Ni '951 publication").

The Examiner has previously determined that Applicants' pending claims have an effective filing date of May 15, 1997. (*See, e.g.*, Office Action mailed June 27, 2006, p. 2). However, the Examiner maintains that the Ni '951 publication's effective filing date is March 17, 1997, the filing date of provisional application 60/040,846 ("the '846 application"), to which the Ni '951 publication claims priority under 35 U.S.C. § 119(e). Applicants traverse the Examiner's rejection of the pending claims under § 102(e) for at least the reasons set forth below.

On August 31, 2005, the Board of Patent Appeals and Interferences ("the Board") declared Interference No. 105,361 ("the '361 Interference") between U.S. Patent No. 6,872,568 to Ni et al. ("the '568 patent") and U.S. Application No. 10/423,448 to Adams et al. ("the '448 application"). Count 1 of the '361 Interference (claim 21 of Ni's '568 patent [claim 134 of Adams' '448 application]) is directed to an isolated monoclonal antibody or fragment thereof that specifically binds to a protein consisting of amino acid residues 1 to 133 of SEQ ID NO:2 [or 52 to 184 of SEQ ID NO:1] wherein said antibody or fragment thereof is an antagonist of the

protein of SEQ ID NO:2 [or of SEQ ID NO:1]. Count 2 of the '361 Interference (claim 20 of Ni's '568 patent [claim 133 of Adams' '448 application]) is directed to an isolated monoclonal antibody or fragment thereof that specifically binds to a protein consisting of amino acid residues 1 to 133 of SEQ ID NO:2 [or 52 to 184 of SEQ ID NO:1] wherein said antibody or fragment thereof is an agonist of the protein of SEQ ID NO:2 [or of SEQ ID NO:1]. In declaring the '361 Interference, the Board determined that Ni was not entitled to priority benefit of any of its earlier filed applications, including the '846 application for the involved Counts. To date, a decision on substantive motions in the '361 Interference has not been received by Applicants.

In a Response and Amendment under 37 C.F.R. § 1.111 dated November 3, 2006, Applicants respectfully submitted that, in view of the Board's initial determination that the Ni '846 application does not support the subject matter of Count 2 in the '361 Interference, the Ni '951 publication cannot be entitled to the benefit of the '846 application's filing date for the claimed subject matter (directed to methods of using an agonist antibody to induce apoptosis or to treat cancer) and, therefore, cannot be effective as prior art against Applicants' pending claims under 35 U.S.C. § 102(e).

In the Office Action dated January 25, 2007, the Examiner acknowledged the Board's initial determinations in the Declaration of the '361 Interference. However, the Examiner noted that "[u]ntil the Board decides the outcome of the interference, it is not established that Ni et al. does not get priority back to the provisional application, 60/040,846."

Initially, Applicants respectfully maintain that it appears inconsistent for the rejection of Applicants' claims to be based on an assumption that is contrary to the initial determination of the Board.

In addition to the Board's determination in the '361 interference, Applicants observe that the Board has subsequently made repeated determinations that the Ni '846 application does not provide an enabled or described embodiment of a nucleotide sequence encoding a DR5 molecule, an amino acid sequence of a DR5 polypeptide, or an antagonist antibody that specifically binds to a DR5 polypeptide.

Specifically, on October 5, 2005, the Board declared Interference No. 105,380 ("the '380 Interference") between U.S. Patent No. 6,569,642 to Rauch et al. ("the '642 patent") and U.S. Application No. 09/042,583 to Ni et al. ("the Ni '583 application"). The Count in the '380 Interference is directed to DNA encoding certain DR5 polypeptides (comprising an amino acid sequence that is at least 90% identical to the amino acid sequence in SEQ ID NO:2 of the '642 patent) which bind TRAIL. The Ni '583 application involved in the '380 Interference is a member of the same family of applications and patents as the Ni '951 publication being applied by the Examiner against the pending claims. In declaring the '380 Interference, the Board determined that the involved Ni '583 application was not entitled to benefit of the '846 application's March 17, 1997, filing date with respect to the Count. On March 9, 2007, the Board affirmed its determination and held that the involved Ni '583 application was not entitled to benefit of the March 17, 1997, filing date of the '846 application with respect to the Count, but was entitled to benefit of the July 29, 1997, filing date of U.S. Application No. 60/054,021 ("the '021 application"). *See, e.g.,* Interference 105,380 Decision-Motions-Bd.R. 125(a) at page 37, lines 1-2 (*i.e.*, "...Ni is not entitled to benefit of the filing date of the '846 application as to Count 1."). A copy of the Board's decision in the '380 Interference is provided herewith as ADE-37.

On October 5, 2005, the Board declared Interference No. 105,381 ("the '381 Interference") between U.S. Patent No. 6,642,358 to Rauch et al. ("the '358 patent") and U.S.

Application No. 10/005,842 to Ni et al. ("the Ni '842 application"). The Count of the '381 Interference was directed to DR5 polypeptides which bind TRAIL (comprising an amino acid sequence that is at least 90% identical to the amino acid sequence presented in SEQ ID NO:2 of the '358 patent.) The Ni '842 application involved in the '381 Interference is a member of the same family of applications and patents as the Ni '951 publication being applied by the Examiner against Applicants' pending claims. In declaring the '381 Interference, the Board determined that the involved Ni et al. application (the '842 application) was not entitled to benefit of the '846 application's March 17, 1997, filing date with respect to the Count of that Interference. On March 26, 2007, the Board affirmed its determination and held that the involved Ni '842 application was not entitled to the benefit of the March 17, 1997, filing date of the '846 application with respect to the Count, but was entitled to benefit of the July 29, 1997, filing date of the '021 application. *See, e.g.,* Interference 105,381 Decision-Motions-Bd.R. 125(a) at page 28, lines 19-20 (i.e., "...Ni is not entitled to benefit for the purpose of priority of the filing date of the '846 application as to Count 1."). Even if Ni was deemed to be entitled to benefit of its July 1997 '021 application, the effective date of Ni's '951 publication is later than Adams's May 1997 effective date. A copy of the Board's decision in the '381 Interference is provided herewith as ADE-38.

On August 31, 2005, the Board declared Interference No. 105,240 ("the '240 Interference") between the Ni et al. '568 patent and U.S. Application No. 09/378,045 to Rauch et al. ("the '045 application"). The Count of the '240 Interference was directed to an antibody that is an antagonist of certain DR5 polypeptides. In declaring the '240 Interference, the Board determined that the involved Ni et al. '568 patent was not entitled to benefit of the '846 application's March 17, 1997, filing date with respect to the involved Count. Indeed, similar to

the '361 Interference, the Board determined that party Ni was not entitled to priority benefit of any earlier-filed application with respect to the involved Count. While Applicants are not aware of any subsequent decision of the Board with respect to the '240 Interference, the above-noted finding plainly is consistent with the other determinations of the Board in the '361, '380, and '381 Interferences; namely, that the Ni family of applications is not entitled to claim the benefit of the filing date of the Ni '846 application.

Applicants respectfully submit that the above-identified determinations by the Board support the Applicants' position that the Ni '951 publication is not entitled to an effective filing date of March 17, 1997, and, therefore, cannot serve as a basis for rejecting Applicants' pending claims under § 102(e). Indeed, in view of these determinations by the Board, the Office has no tenable basis for maintaining the rejection of Applicants' pending claims under 35 U.S.C. § 102(e) based on applications or patents that seek to claim benefit of the March 17, 1997, filing date of the '846 application.

In view of the above, Applicants respectfully request withdrawal of the outstanding rejection and issuance of the pending claims.

II. Suggestion of Interference

In the event Applicants' pending claims are considered allowable, but not in condition for issuance, Applicants further suggest the declaration of an interference between the present application (U.S. Application No. 10/052,798 to Adams et al.; "the '798 application") and U.S. Patent Application No. 10/648,825 to Ni et al. ("the '825 application") in accordance with the provisions of 37 C.F.R. § 41.202(d).

The procedural status of the '798 and '825 applications is discussed briefly below. In addition to providing information and explanations in accordance with 37 C.F.R. § 41.202(d),

Applicants provide four proposed PTO-850 forms (as Appendices A1-A4) reflecting the alternative procedural structures discussed herein.

For the purposes of this suggestion, the designations "DR5" and "Apo-2" are used to refer to the same receptor molecule. The designations are used interchangeably.

A. Procedural Status of the Involved Applications

1. Status of the '798 Application to Adams et al.

As explained above, a Final Office Action was entered in the '798 application on January 25, 2007. Claims 59, 60, 65, 66, 69-74, 79, 125, 127-129, 133, 135-137, and 147-155 are pending in the application and stand rejected under 35 U.S.C. § 102(e) as being anticipated by the Ni '951 publication. The claims of the '798 application are directed to, *inter alia,* methods of inducing apoptosis in mammalian cancer cells comprising exposing mammalian cancer cells to an effective amount of an Apo-2 agonist monoclonal antibody which (a) binds to a soluble extracellular domain sequence of an Apo-2 polypeptide consisting of amino acids 54 to 182 of SEQ ID NO:1 and (b) induces apoptosis in at least one type of mammalian cancer cell *in vivo* or *ex vivo*. Notwithstanding the Examiner's finding of interfering subject matter between the claims of the '798 application and the Ni '825 application, the claims in the '798 application have been found to be in condition for allowance.

2. Status of the '825 Application to Ni et al.

On December 20, 2006, an *ex parte Quayle* Action was entered in the '825 application. Claims 78-91, 134-145, 182-195, and 238-249 are pending in the application. All claims are indicated as being in condition for allowance except for an objection to claims 182-195 and 238-249. Specifically, the Examiner objected to claims 182-195 and 238-249 under 37 C.F.R. § 1.75 as being substantial duplicates of claims 78-91 and 134-145, respectively. The claims in the Ni

'825 application are directed to, *inter alia,* a method of inducing apoptosis of a DR5-expressing cell, comprising contacting said cell with an agonist antibody or fragment thereof that specifically binds to a polypeptide consisting of amino acids 1 to 133 of SEQ ID NO:2.

3. Order dated March 28, 2007, in Interference No. 105,361

The '361 Interference is presently pending before the Board and the parties are awaiting a decision on preliminary motions.

On March 28, 2007, Administrative Patent Judge Richard E. Schafer ("Judge Schafer") entered an Order - Bd. R. 104(a) (Paper No. 103) summarizing a conference call held on March 13, 2007, between Judge Schafer and counsel for both parties in the '361 Interference. During the call, each party sought permission to file a motion seeking to change the subject matter of the '361 Interference. Party Ni sought authorization to file a motion to add the Adams '798 and Ni '825 applications to the Interference. Party Adams sought authorization to file a motion to declare an additional interference between the '798 and '825 applications. Judge Schafer did not authorize the requested motions, noting that "[n]either application was in condition for allowance, although it was represented that the applications would be in condition for allowance soon." Judge Schafer further noted that "the examiners assigned to the applications are aware of the potential interference" and that the parties are required to file a notice in the '361 Interference when their respective *ex parte* applications are in condition for allowance. A copy of the Order is provided herewith as ADE-39.

B. Relevant Interference Rules

37 C.F.R. § 41.202 sets forth the requirements for an Applicant suggesting an interference between an application and another application or patent. Specifically, 37 C.F.R. § 41.202(a) requires a suggestion for interference to:

(1) Provide sufficient information to identify the application or patent with which the applicant seeks an interference;

(2) Identify all claims the applicant believes interfere, propose one or more counts, and show how the claims correspond to one or more counts;

(3) For each count, provide a claim chart comparing at least one claim of each party corresponding to the count and show why the claims interfere within the meaning of § 41.203(a);

(4) Explain in detail why the applicant will prevail on priority;

(5) If a claim has been added or amended to provoke an interference, provide a claim chart showing the written description for each claim in the applicant's specification; and

(6) For each constructive reduction to practice for which the applicant wishes to be accorded benefit, provide a chart showing where the disclosure provides a constructive reduction to practice within the scope of the interfering subject matter.

Applicant provides information regarding these issues in the present suggestion for interference in compliance with 37 C.F.R. § 41.202.

C. <u>Appendices</u>

Several appendices are provided to facilitate the review of this request for interference and to comply with the procedural requirements of 37 C.F.R. § 41.202. A brief description of each appendix is provided below.

Appendix A: Form PTO-850

Appendix A1: Form PTO-850 – Adams *et al.* is Senior Party

Appendix A2: Form PTO-850 – Adams *et al.* is Senior Party

Appendix A3: Form PTO-850 – Adams *et al.* is Senior Party

Appendix A4: Form PTO-850 – Adams *et al.* is Junior Party

Appendix B: Applicants' Pending Claims, *i.e.*, Claims 59, 60, 65, 66, 69-74, 79, 125, 127-129, 133, 135-137, and 147-155

Appendix C: Pending Claims of U.S. Patent Application No. 10/648,825 to Ni *et al.*, *i.e.*, Claims 78-91, 134-145, 182-195, and 238-249

Appendix D: Comparison of Amino Acid Residues 54-182 of Applicants' SEQ ID NO:1 and Amino Acid Residues 3-131 of Ni's '825 application SEQ ID NO:2

Appendix E: Chart: Earlier-filed Adams *et al.* Applications

Appendix F: Constructive Reduction to Practice of the Proposed Count in 60/046,615 Specification

Appendix G: Constructive Reduction to Practice of the Proposed Count in 60/074,119 Specification

Appendix H: Constructive Reduction to Practice of the Proposed Count in 09/079,029 Specification

Appendix I: Constructive Reduction to Practice of the Proposed Count in 10/052,798 Specification

Appendix J: List of Documentary Exhibits Supporting the Request for Interference

III. 37 C.F.R. § 41.202(a)(1) - Identification of Application

Applicants request the declaration of an interference between Applicants' present application, *i.e.*, the '798 application, and the '825 application to Ni *et al.*

IV. 37 C.F.R. § 41.202(a)(2) – Identification of Interfering Claims, Proposed Count, and Claim Correspondence

A. Identification of Interfering Claims

In accordance with the requirements of 37 C.F.R. § 41.202(a)(2), Applicants submit that an interference exists between at least claim 65 of Applicants' '798 application and claim 83 of Ni's '825 application. In other words, Applicants' claim 65, if prior art, would have anticipated or rendered obvious the subject matter of Ni claim 83 and *vice-versa*. 37 C.F.R. § 41.203(a).

B. Proposed Count

37 C.F.R. § 41.201 provides the following definition of the term "count":

> *Count* means the Board's description of the interfering subject matter that sets the scope of admissible proofs on priority.

In accordance with the requirements of 37 C.F.R. § 41.202(a)(2), the proposed Count is defined in the alternative as Applicants' claim 65 or Ni's '825 application claim 83. In other words, the proposed Count is directed to a method of inducing apoptosis in mammalian cancer cells comprising exposing mammalian cancer cells to an effective amount of an Apo-2 agonist monoclonal antibody which (a) binds to a soluble extracellular domain sequence of an Apo-2 polypeptide consisting of amino acids 54 to 182 of SEQ ID NO:1 and (b) induces apoptosis in at least one type of mammalian cancer cell *in vivo* or *ex vivo*. It is noted that Applicants' claim 65 recites amino acid residues 54-182 of SEQ ID NO:1, whereas Ni's '825 application claim 83 recites amino acid residues 1-133 of SEQ ID NO:2. As illustrated in Appendix D, amino acid residues 54-182 of Applicants' SEQ ID NO:1 are the same as amino acid residues 3-131 of Ni's '825 application SEQ ID NO:2.

In accordance with 37 C.F.R. § 41.202(a)(3), the claim chart below compares Applicants' claim 65 and Ni's '825 application claim 83 (set forth in independent form), which alternatively define the proposed Count and should be designated as corresponding thereto.

Applicants' '798 Application Claim 65	**Ni's '825 Application Claim 83**
A method of inducing apoptosis in mammalian cancer cells comprising	A method of inducing apoptosis of a DR5-expressing cell, comprising
exposing mammalian cancer cells to an effective amount of an Apo-2 agonist monoclonal antibody which	contacting said cell with an agonist antibody or fragment thereof that
(a) binds to a soluble extracellular domain sequence of an Apo-2 polypeptide consisting of amino acids 54 to 182 of SEQ ID NO:1 and	specifically binds to a polypeptide consisting of amino acids 1 to 133 of SEQ ID NO:2, wherein said antibody or fragment thereof is monoclonal.
(b) induces apoptosis in at least one type of mammalian cancer cell *in vivo* or *ex vivo*.	

Amino acid residues 54-182 of Applicants' SEQ ID NO:1 correspond to amino acid residues 3-131 of Ni's '825 application SEQ ID NO:2.

Applicants' claim 65, if prior art, would have anticipated or rendered obvious Ni's '825 application claim 83 and *vice-versa*. Therefore, at least these two claims are believed to "interfere" within the meaning of 37 C.F.R. § 41.203(a).

C. Correspondence of Claims to the Proposed Count

Under the provisions of 37 C.F.R.§ 41.207(b)(2), a claim corresponds to a count if the subject matter of the count, treated as prior art to the claim, would have anticipated or rendered obvious the subject matter of the claim.

The claims of the parties that are believed to correspond to the proposed Count are as follows:

The '798 Application Claims (Adams *et al.*): Claims 59, 60, 65, 66, 69-74, 79, 125, 127-129, 133, 135-137, and 147-155

The '825 Application Claims (Ni *et al.*): Claims 78-91, 134-145, 182-195, and 238-249

The claims of the parties that are believed to not correspond to the proposed Count are as follows:

The '798 Application Claims (Adams *et al.*): none

The '825 Application Claims (Ni *et al.*): none

A method of inducing apoptosis in mammalian cancer cells comprising exposing mammalian cancer cells to an effective amount of an Apo-2 agonist monoclonal antibody which (a) binds to a soluble extracellular domain sequence of an Apo-2 polypeptide consisting of amino acids 54 to 182 of SEQ ID NO:1 and (b) induces apoptosis in at least one type of mammalian cancer cell *in vivo* or *ex vivo*, treated as prior art to each of the '798 and '825 application claims, would have anticipated or rendered obvious the subject matter of each of these claims.

V. 37 C.F.R. §§ 41.202 (a)(4) and 41.202(d) – Applicants will Prevail on Priority

A. Overview

Applicants will prevail on priority with respect to the proposed Count for at least three

reasons, taking into consideration the respective filing dates of Applicants' applications (filed in May 1997, February 1998, and May 1998) and Ni *et al.*'s applications (filed in March 1997, July 1997, March 1998, and May 2000).

In May 1998, Applicants constructively reduced to practice an embodiment within the scope of the proposed Count. Assuming the Ni *et al.* applications filed in March 1997 ('846 application), July 1997 ('021 application), or March 1998 ('583 application) do not constitute a constructive reduction to practice of the proposed Count, then Applicants' May 1998 application ('029 application) constitutes a prior constructive reduction to practice of the proposed Count. Accordingly, Applicants should be Senior Party. (Appendix A1).

If Ni *et al.*'s application filed in March 1998 ('583 application) is considered to be a constructive reduction to practice of the proposed Count, then Applicants' February 1998 application ('119 application) constitutes a prior constructive reduction to practice of the proposed Count. Accordingly, Applicants should be Senior Party. (Appendix A2).

If Ni *et al.*'s application filed in July 1997 ('021 application) is considered to be a constructive reduction to practice of the proposed Count, then Applicants' May 1997 application ('615 application) constitutes a prior constructive reduction to practice of the proposed Count. Accordingly, Applicants should be Senior Party. (Appendix A3).

If Ni *et al.*'s application filed in March 1997 ('846 application) is considered to be a constructive reduction to practice of the proposed Count, then Applicants conceived of embodiments within the scope of the proposed Count prior to the filing of Ni *et al.*'s March 1997 application and Applicants thereafter exercised reasonable diligence in constructively reducing to practice such embodiments by filing Applicants' May 1997 application ('615 application) . Applicants would be Junior Party. (Appendix A4).

B. The Proposed Count

The proposed Count is defined in the alternative as Applicants' claim 65 or Ni's '825 application claim 83. In other words, the proposed Count is directed to a method of inducing apoptosis in mammalian cancer cells comprising exposing mammalian cancer cells to an effective amount of an Apo-2 agonist monoclonal antibody which (a) binds to a soluble extracellular domain sequence of an Apo-2 polypeptide consisting of amino acids 54 to 182 of SEQ ID NO:1 and (b) induces apoptosis in at least one type of mammalian cancer cell *in vivo* or *ex vivo*.

C. Relevant Legal Principles

1. Relevant Interference Rules Regarding "Accorded Benefit" and "Constructive Reduction to Practice"

37 C.F.R. § 41.207(a)(1) states that "Parties are presumed to have invented interfering subject matter in the order of the dates of their accorded benefit for each count."

37 C.F.R. § 41.201 states that "*Accord benefit* means Board recognition that a patent application provides a proper constructive reduction to practice under 35 U.S.C. § 102(g)(1)."

37 C.F.R. § 41.201 further states that "*Constructive reduction to practice* means a described and enabled anticipation under 35 U.S.C. § 102(g)(1) in a patent application of the subject matter of a count."

37 C.F.R. § 41.201 also states that "*[e]arliest constructive reduction to practice* means the first constructive reduction to practice that has been continuously disclosed through a chain of patent applications, including in the involved application or patent. For the chain to be continuous, each subsequent application must have been co-pending under 35 U.S.C. 120 or 121 or timely filed under 35 U.S.C. 119 or 365(a)."

2. Relevant Case Law Regarding Constructive Reductions to Practice and Written Description

For a party in an interference to obtain the benefit of the filing date of an earlier-filed application for the purpose of priority, the earlier-filed application must contain a written description of the subject matter of the interference count. *Hyatt v. Boone*, 146 F.3d 1348, 1352, 47 U.S.P.Q.2d 1128, 1130 (Fed. Cir. 1998). In *Hyatt*, the court stated that "[f]or an earlier-filed application to serve as a constructive reduction to practice of the subject matter of an interference count, the applicant must describe the subject matter of the count in terms that establish that he was in possession of the later-claimed invention, including all of the elements and limitations presented in the count, at the time of the earlier filing." 146 F.3d at 1354, 47 U.S.P.Q.2d at 1131. The *Hyatt* court emphasized that:

> [W]hen an explicit limitation in an interference count is not present in the written description whose benefit is sought it must be shown that a person of ordinary skill would have understood, at the time the patent application was filed, that the description requires that limitation. As discussed in *Martin v. Mayer*, 823 F.2d 500, 505, 3 U.S.P.Q.2d 1333, 1337 (Fed. Cir. 1987), "It is 'not a question of whether one skilled in the art might be able to construct the patentee's device from the teachings of the disclosure... Rather, it is a question whether the application necessarily discloses that particular device.'" It is insufficient as written description, for purposes of establishing priority of invention, to provide a specification that does not unambiguously describe all limitations of the count. [citation omitted]

Id. (internal citations omitted).

Compliance with the written description requirement of 35 U.S.C. § 112, first paragraph, requires a description of the composition recited in the claims. "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Regents of the University of California v. Eli*

Lilly and Co., 119 F.3d 1559, 1567, 43 U.S.P.Q.2d 1398, 1405 (Fed. Cir. 1997)(citing *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 U.S.P.Q.2d 1601, 1606 (Fed. Cir. 1993). In *Lilly*, the Federal Circuit noted the following:

> a generic statement such as... "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function...does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. at 1568, 43 U.S.P.Q.2d at 1406. The greater the degree of unpredictability in the technological field of the invention, the greater the need is for a written description that sets forth with particularity the precise nature of the structure or structures that a compound must have to exhibit a particular, recited functional property. Moreover, as the Federal Circuit held in *Enzo v. Gen-Probe*, 323 F.3d 956, 968, 63 U.S.P.Q.2d 1609, 1616 (Fed. Cir. 2002):

> We next address Enzo's additional argument that the written description requirement for the generic claims is necessarily met as a matter of law because the claim language appears *in ipsis verbis* in the specification. We do not agree. Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. One may consider examples from the chemical arts. A description of an anti-inflammatory steroid, *i.e.,* a steroid (a generic structural term) described even in terms of its function of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function. Similarly, the expression "an antibiotic penicillin" fails to distinguish a particular penicillin molecule from others possessing the same activity. A description of what a material does, rather than of what it is, usually does not suffice. *Eli Lilly,* 119 F.3d at 1568, 43 USPQ2d at 1406. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Id.*

D. Applicants Constructively Reduced to Practice the Proposed Count Prior to Ni *et al.*

1. Applicants' '029 Application Provides a Constructive Reduction To Practice of the Proposed Count

On May 14, 1998, Applicants filed an application (U.S. Application No. 09/079,029; "the '029 application") fully describing the structure, name, formula, and definitive chemical and physical properties of several monoclonal antibodies including, for example, antibodies designated 3F11.39.7, 16E2, 20E6 and 24C4. (*See, e.g.*, Examples 9, 10, 12-16 at pp. 74-76, 78-89; Figs. 7-9, and 11-14, p. 11, ll. 13-22 and p. 11, l. 26 to p. 12, l. 21). Applicants deposited 3F11.39.7 with the ATCC on January 13, 1998 (ATCC Deposit No. HB-12456). (*See*, p. 89, l. 8). The nucleic acid sequences of the variable domains of 16E2, 20E6 and 24C4 are set forth in the '029 specification as shown in SEQ ID NO:6, SEQ ID NO:7, and SEQ ID NO:8, respectively (in FIGS. 15A, 15B and 15C, respectively). (*See*, p. 12, ll. 22-27, and p. 82, ll. 30-33).

The working examples set forth in the '029 application demonstrate that, for example, 3F11.39.7, 16E2 and 20E6 bind to a soluble extracellular domain sequence of an Apo-2 polypeptide consisting of amino acids 54 to 182 of SEQ ID NO:1 and induce apoptosis in at least one type of mammalian cancer cell. The immunogen used consists of amino acids 1-184 of Apo-2. As disclosed in the application, a putative signal sequence of Apo-2 includes amino acids 1-53 and a putative extracellular domain includes amino acids 54-182. The signal sequence is cleaved to yield the extracellular domain. (*See, e.g.*, p. 11, ll. 13-22 and 26-34; p. 12, ll. 1-21; p. 76, ll. 9-35; p. 78, ll. 5-14; p. 79, l. 5 to p. 85, l. 7; p. 85, l. 10 to p. 88, l. 36; FIGS. 7-9, 11-12B, and 13A-14C).

Appendix H is a claim chart illustrating the disclosure in the '029 application that satisfies each limitation of the proposed Count. Accordingly, the '029 application provides a

2. Applicants' '119 Application Provides a Constructive Reduction To Practice of the Proposed Count

On February 9, 1998, Applicants filed an application (U.S. Application No. 60/074,119; "the '119 application") fully describing the structure, name, formula, and definitive chemical and physical properties of the monoclonal antibody 3F11.39.7, as described above. (*See, e.g.*, p. 47, ll. 20-41; Examples 9, 10, 12, 13 at pp. 64-66 and 68; FIGS. 7-9, 11, and p. 10, ll. 28-37; p. 10, l. 40 to p. 11, l. 1). Applicants deposited 3F11.39.7 with the ATCC on January 13, 1998 (ATCC Deposit No. HB-12456) (p. 69, l. 9).

The working examples set forth in the '119 application demonstrate that, for example, the monoclonal antibody 3F11.39.7 binds to a soluble extracellular domain sequence of an Apo-2 polypeptide consisting of amino acids 54 to 182 of SEQ ID NO:1 and induces apoptosis in at least one type of mammalian cancer cell. The immunogen used consists of amino acids 1-184 of Apo-2. As disclosed in the application, a purported signal sequence of Apo-2 includes amino acids 1-53 and a purported extracellular domain includes amino acids 54-182. The signal sequence is cleaved to yield the extracellular domain. (*See, e.g.*, p. 10, ll. 28-37; p. 10, l. 40 to p. 11, l. 1; p. 66, ll. 18-39; p. 68, ll. 8-16; FIGS. 7-9, and 11).

Appendix G is a claim chart illustrating the disclosure in the '119 application that satisfies each limitation of the proposed Count. Accordingly, the '119 application provides a constructive reduction to practice of the proposed Count.

3. None of Ni et al.'s '846, '021, or '583 Applications Provide a Constructive Reduction to Practice of the Proposed Count

Prior to the filing date of Applicants' '119 application, Ni *et al.* filed two provisional applications, (U.S. Application No. 60/040,846; "the '846 application"; filed on March 17, 1997)

and (U.S. Application No. 60/054,021; "the '021 application"; filed on July 29, 1997) and one non-provisional application (U.S. Application No. 09/042,583; "the '583 application"; filed on March 17, 1998).

Each of Ni's '846, '021, and '583 applications acknowledges that the DR5 polypeptide is a member of a class of polypeptides whose biological functions are highly unpredictable. ("Tumor Necrosis Factor (TNF) family ligands are known to be among the most pleiotropic cytokines, inducing a large number of cellular responses..." (*See,* page 3 of the '846 application and page 4 of the '021 and '583 applications)).

None of Ni's '846, '021, and '583 applications provides a description of the structure, name, formula, or definitive chemical and physical properties of a specific monoclonal antibody or fragment thereof that specifically binds to a polypeptide consisting of amino acids 1 to 133 of SEQ ID NO:2. Likewise, none of Ni's '846, '021, and '583 applications provides a working example wherein a DR5-expressing cell is contacted with a specific monoclonal agonist antibody or fragment thereof that specifically binds to a polypeptide consisting of amino acids 1 to 133 of SEQ ID NO:2. Finally, none of Ni's '846, '021, and '583 applications provides a working example wherein apoptosis is induced by contacting a DR5-expressing cell with a specific monoclonal agonist antibody or fragment thereof that specifically binds to a polypeptide consisting of amino acids 1 to 133 of SEQ ID NO:2.

Ni *et al.*'s specifications filed prior to Applicants' '119 and/or '029 applications reflect, at most, mere speculation of an unspecified and uncharacterized "agonist" antibody to a DR5 polypeptide. However, mere research plans or hopes for obtaining a chemical composition having a specific biological function (*e.g.*, an agonist antibody) are not sufficient to establish a conception or a reduction to practice of the chemical composition. *Fiers v. Revel*, 984 F.2d at

The Ni *et al.* specifications clearly reflect that neither Ni *et al.*, nor one of ordinary skill in the art, could have envisioned the detailed chemical structure of an agonist antibody to DR5 polypeptide based on the disclosure in Ni *et al.*'s '846 and '021 specifications. Indeed, Ni *et al.*'s '846 disclosure does not even provide insight into any physical characteristics of a ligand which must bind to DR5 polypeptide to induce the specified agonistic function of the DR5 polypeptide receptor.

In view of the above, Applicants maintain that none of Ni's '846, '021, and '583 applications constitutes a constructive reduction to practice of the proposed Count. Applicants' '119 and '029 applications constitute constructive reductions to practice prior to any effective filing date of Ni. Accordingly, Applicants are entitled to judgment on the issue of priority because Applicants constructively reduced to practice an embodiment within the scope of the proposed Count prior to Ni *et al.* Applicants, therefore, should be designated as the Senior Party in the requested Interference.

E. If Ni *et al.'s* '021 Application, filed July 1997 Constitutes a Constructive Reduction to Practice of The Proposed Count, Then Applicants' '615 Application, filed May 1997 Constitutes a Prior Constructive Reduction to Practice of the Proposed Count

On May 15, 1997, Applicants filed an application (U.S. Application No. 60/046,615; "the '615 Application") wherein Applicants disclosed a polynucleotide sequence encoding the Apo-2 polypeptide (Figure 1; SEQ ID NO:2). The '615 application contains disclosure relating to, *inter alia*, anti-Apo-2 antibodies (starting at page 47, line 25), including monoclonal antibodies (page 48, line 20 to page 51, line 31) and therapeutic uses of Apo-2 antibodies (page 17, lines 13-15; page 44, lines 11-12; page 45, lines 1-10; page 53, lines 7-9 and 21-23; page 56, line 20 to page

57, line 23; and page 57, lines 25-28). Applicants provided disclosures relating to agonist and antagonist antibodies. (*See, e.g.*, page 10, lines 3-5 and 8-9; page 16, line 34 to page 17, line 3; and page 56, lines 22-27). Applicants also identified a specific ligand which binds an Apo-2 polypeptide, and the biological functional consequences of such binding. (*See, e.g.*, page 63, line 11 to page 64, line 6; page 65, lines 16-28).

Applicants' '615 application does not describe a specific example of a monoclonal agonist antibody for DR5, such as the 3F11.39.7 monoclonal antibody subsequently described in Applicants' '119 application or the 16E2 monoclonal antibody subsequently described in Applicants' '029 application.

Above, Applicants maintain that Ni *et al.* is not entitled to the benefit of any of its '846, '021, or '583 applications with respect to the proposed Count because none of these Ni *et al.* applications specifically describe a monoclonal agonist antibody for Apo-2/DR5 or exemplify the use of such an antibody to induce apoptosis. Thus, these Ni *et al.* applications do not constitute a constructive reduction to practice of an embodiment within the scope of the proposed Count.

Nonetheless, in the event the Examiner considers Ni *et al.*'s '021 application, filed on July 29, 1997, to be a constructive reduction to practice of the proposed Count, then Applicants' '615 application, filed on May 15, 1997, should be found to constitute a prior constructive reduction to practice of the proposed Count because Applicants' '615 application discloses at least as much as the Ni et al. '021 application does. Applicants' '615 application, for example, discloses the identity of a specific ligand that binds to the Apo-2 polypeptide, the complete sequence of the Apo-2 polypeptide, characterization of the various regions of the Apo-2 polypeptide, the functional consequences of Apo-2 ligand binding to cells expressing the Apo-2

receptor polypeptide and other information relevant to the properties of antibodies that act as antagonists and agonists to the Apo-2 receptor polypeptide. Accordingly, Applicants would be entitled to judgment on priority for the proposed Count. Applicants should be designated as the Senior Party in the requested interference.

F. If Ni *et al.*'s '846 Application, Filed March 1997, Is Considered To Be A Constructive Reduction To Practice Of The Proposed Count, Then Applicants Conceived Of Embodiments Within The Scope Of The Proposed Count Prior To Ni *et al.*'s March 1997 Application And Applicants Thereafter Exercised Reasonable Diligence In Constructively Reducing To Practice Such Embodiments By Filing Applicants' May 1997 Application.

In the event the Examiner determines that Ni *et al.*'s '846 application constitutes a constructive reduction to practice of the proposed Count, then Applicants will prevail on priority because Applicants should be determined to have conceived of the subject matter of the proposed Count prior to March 17, 1997, and to have exercised reasonable diligence in constructively reducing to practice such subject matter in the '615 application, filed on May 15, 1997.

The Apo-2 receptor characterization work conducted by Dr. Ashkenazi and those working on his behalf beginning prior to March 17, 1997, until May 15, 1997, is described in Examples 1 through 8 in the '615 application. Examples 1 through 8 describe experiments directed to: a) identifying, isolating, cloning, and sequencing the DNA sequence encoding the Apo-2 receptor (Example 1); b) construction of vectors encoding Apo-2-Flag, Apo-2-IgG, and Apo-2-GST fusion proteins for use in binding and/or purification studies (Examples 2, 3, and 4); c) overexpressing a vector encoding the Apo-2 receptor in a cell based system to determine whether overexpression of the receptor induces apoptosis (Example 4); d) conducting binding studies using the Apo-2-IgG and Apo-2-Flag fusion proteins and the Apo-2 ligand (Example 5); e) conducting experiments to evaluate whether the newly identified Apo-2 receptor activates the

NFκB pathway (Example 6); f) evaluating tissue localization of the Apo-2 mRNA using northern blot analyses (Example 7); and g) conducting chromosomal mapping experiments to map the location of the gene encoding the Apo-2 receptor (Example 8). (ADE-18).

Specifically, the '615 application discloses the therapeutic applications using Apo-2 antibodies, as well as articles of manufacture and kits containing Apo-2 antibodies. (*See*, p. 57, ll. 25-28). For example, Apo-2 antibodies can be employed therapeutically to induce apoptosis in mammalian cells. (*See*, p. 45, pp. 1-5).

The activities described in the concurrently submitted declarations of Dr. Ashkenazi, Dr. Wood, Mr. Marsters, Mr. Pitti, and Dr. Sheridan describe in detail the activities relating to the subject matter described in Examples 1-8. These activities were continuous and were conducted from prior to March 17, 1997, until the filing of Applicants' earliest filed application. (ADE-1, ADE-3, ADE-4, ADE-5, and ADE-6).

The initial database searches, probe design, and clone isolations described in Example 1 of the '615 application, correspond to the work described in the declarations of Dr. Wood, Dr. Ashkenazi, and Mr. Marsters, submitted herewith. (ADE-1, ADE-3, ADE-6, and ADE-18). Most of this work was conducted prior to March 17, 1997. Experiments conducted after March 17, 1997, and prior to May 15, 1997, involving studies confirming expression of Apo-2 receptor DNA, are described in Mr. Marsters' declaration at paragraphs 313-339. (ADE-6). Additional experiments directed to inserting the Apo-2 receptor DNA into vectors are described in Mr. Marsters' declaration at paragraphs 401-424. (ADE-6).

The construction, expression, and characterization of Apo-2-ECD-Flag and Apo-2-IgG fusion constructs described in Example 2 of the '615 application, correspond to the work described in the declarations of Mr. Marsters, Mr. Pitti, and Dr. Sheridan, submitted herewith.

(ADE-4, ADE-5, ADE-6, and ADE-18). Specifically, work conducted from prior to March 17, 1997, until May 15, 1997, is described, *e.g.*, at paragraphs 115-141 of Mr. Pitti's Declaration (ADE-4), and paragraphs 106-125, 146-156, 172-183, 196-250, 268-275, 283-285, and 340-400 of Mr. Marsters' Declaration (ADE-6).

The Apo-2-ECD-Flag – Apo-2 ligand binding studies described in Example 3 of the '615 application, correspond to the work described in the declarations of Mr. Pitti and Mr. Marsters, submitted herewith. (ADE-4, ADE-6, and ADE-18). Specifically, work conducted from prior to March 17, 1997, until May 15, 1997, is described, *e.g.*, at paragraphs 142-147, 165-170, 188-192, and 194-206 of Mr. Pitti's Declaration (ADE-4), and paragraphs 259-267 and 276-282 of Mr. Marsters' Declaration (ADE-6).

The expression assays using the construct encoding the Apo-2 receptor described in Example 4 of the '615 application, correspond to the work described in the declarations of Mr. Pitti, Mr. Marsters, and Dr. Sheridan, submitted herewith. (ADE-4, ADE-5, ADE-6, and ADE-18). Specifically, work conducted from prior to March 17, 1997, until May 15, 1997, is described, *e.g.*, at paragraphs 20-114 of Mr. Pitti's Declaration, and paragraphs 76-124 and 157-240 of Dr. Sheridan's Declaration. (The associated work of Mr. Marsters was conducted prior to March 17, 1997). (ADE-4, ADE-5, and ADE-6).

The Apo-2-ECD-Flag and Apo-2-IgG – Apo-2 ligand binding competition studies described in Example 5 of the '615 application, correspond to the work described in the declarations of Mr. Pitti and Dr. Sheridan, submitted herewith. (ADE-4, ADE-5, and ADE-18). Specifically, work conducted from prior to March 17, 1997, until May 15, 1997, is described, *e.g.*, at paragraphs 148-164, 171-187, and 193-198 of Mr. Pitti's Declaration (ADE-4), and paragraphs 125-156 of Dr. Sheridan's Declaration (ADE-5).

The NFκB studies described in Example 6 of the '615 application, correspond to the work described in the declaration of Mr. Marsters and Dr. Sheridan. (ADE-5, ADE-6, and ADE-18). Specifically, work conducted from prior to March 17, 1997, until May 15, 1997, is described, *e.g.*, at paragraphs 126-145, 157-169, 184-195, and 251-258 of Mr. Marsters' Declaration (ADE-6) and paragraphs 48-64, 76-87, 165-170, and 179-201 of Dr. Sheridan's Declaration (ADE-5).

The Northern analyses described in Example 7 of the '615 application correspond to the work described in Mr. Marsters' Declaration. (ADE-6 and ADE-18). This work was conducted prior to March 17, 1997.

The chromosomal mapping experiments described in Example 8 of the '615 application correspond to the work described in the declaration of Mr. Marsters. (ADE-6 and ADE-18). Specifically, this work was conducted from prior to March 17, 1997, and is described, *e.g.*, at paragraphs 97-105 and 309-312 of Mr. Marsters' Declaration. (ADE-6).

Patent counsel for Applicants began drafting a patent application, including the subject matter described in Examples 1-8 of the '615 application, by no later than May 5, 1997, and was diligent in continuing to work on the application until its filing on May 15, 1997. The activities directed to preparing and filing the first-filed application (*i.e.*, the '615 application) involved in this case are described in the Declaration of Diane Marschang at paragraphs 7-29. (ADE-2).

In conclusion, to the extent Ni *et al.*'s '846 application is determined to be a constructive reduction to practice, then Applicants should be considered to have conceived of the subject matter of the proposed Count prior to the filing date of Ni *et al.*'s '846 application and to have exercised reasonable diligence in constructively reducing to practice the invention in Applicants' '615 application. Applicants' submission in support of this request for interference would also

be effective to overcome any applicability of the '951 publication as a reference against Applicants' claims 59, 60, 65, 66, 69-74, 79, 125, 127-129, 133, 135-137, and 147-155 under 35 U.S.C. § 102(e).

VI. 37 C.F.R. § 41.202(a)(5) – Written Description for each Claim in Applicants' Specification

Applicants' claims 59, 60, 65, 66, 69-74, 79, 125, 127-129, 133, 135-137, and 147-155 were not presented or amended for the purpose of provoking an interference with the Ni '825 application. Indeed, Applicants maintain that the pending claims should be issued to Applicant prior to the declaration of any potential interference proceeding. The claims have been considered by the Examiner and have been deemed to be in condition for allowance, but for the outstanding rejection under 35 U.S.C. § 102(e). Therefore, it has already been determined that each of Applicants' claims fully complies with the written description requirement of 35 U.S.C. § 112, first paragraph.

VII. 37 C.F.R. § 41.202(a)(6) – Applicants' Earliest Constructive Reduction to Practice

As reflected in Appendix G, Applicants' '119 application, filed on February 9, 1998, is considered to be Applicants' earliest constructive reduction to practice of the proposed Count, assuming that Ni is not entitled to the benefit of at least any of the '846, '021, or '583 applications with respect to the proposed Count. In the event any one of Ni's '846, '021, or '583 applications is considered to be a constructive reduction to practice of the proposed Count, then Applicants' '615 application, filed on May 15, 1997, is considered to be Applicants' earliest constructive reduction to practice of the proposed Count. Appendices F and H further reflect that Applicants' earliest constructive reduction to practice has been continuously disclosed through a chain of applications. Appendix F reflects text and examples in the disclosure of the 60/046,615

application that demonstrate Applicants constructive reduction to practice of the proposed Count; and Appendix H reflects text and examples of the disclosure of the 09/079,029 application that demonstrate Applicants constructive reduction to practice of the proposed Count. Each application subsequent to the '615 application was a continuation co-pending under 35 U.S.C. § 120. (37 C.F.R. § 201).

VIII. Conclusion

In view of the above, Applicants respectfully request the Examiner to withdraw the outstanding rejection under 35 U.S.C. § 102(e) and proceed to issue the claims pending in the present application. As a contingent request, Applicants request that the Examiner advance this case to the Board of Patent Appeals and Interferences for the declaration of an interference between Applicants' '798 application and the Ni *et al.* '825 application. Applicants respectfully request the Examiner to handle this matter on an expedited basis.

No new fees are believed to be due with the filing of this document. However, if the Patent Office determines that extensions and/or other relief is required, Applicants hereby petition for any such required relief, including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or fees due to our Deposit Account No. **18-1260**, referencing Docket No. **22338-904**. Any refund should be credited to the same account. The Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,
For GENENTECH, INC.

Date: April 24, 2007

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